



Literature alert

July 2026

The second summer edition highlights several studies of interests for andrologists. Among the entries in this edition – the latest EAA clinical practice guidelines on testicular biopsy, controlled treatment trials in infertile men, steatotic liver disease and hypogonadism, low testosterone and stress, cardiometabolic dysfunction in Klinefelter syndrome, maternal environment and risk of testicular cancer, ageing of spermatogenesis, genetic consequences of gorilla's lack of sperm competition, progress in making sperm from blood cells, the evolution of germ cell chromatin architecture, paternal diet and offspring's development, pathways in mouse spermiogenesis, a new atlas of hormone-active (producing and responding) cells, and even a sperm racetrack. Enjoy the summer learning!

Clinical andrology and epidemiology

The latest clinical practice guidelines endorsed by the EAA have been published!

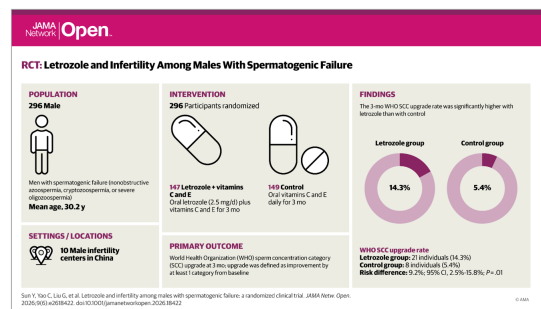
ANDROLOGY



The guidelines concern the indications for testicular biopsies for diagnostic and combined therapeutic-diagnostic purposes as well as recommendations on technical aspects of tissue sampling. The recommendations (34 in total) are based on published evidence, and prepared using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, by a group of interdisciplinary experts, including surgery, fertility management and pathology. The final version was approved by the directors of 29 EAA-accredited andrological centers.

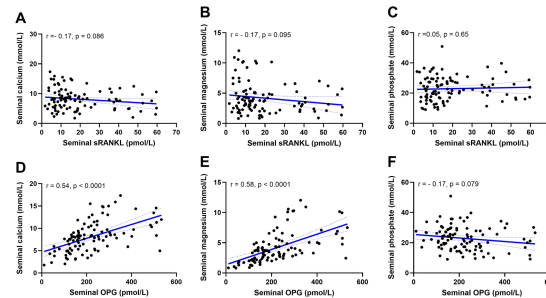
Aksglaede L, Kanakis G, Rajpert-De Meyts E, Jezek D, Algaba F, Dohle G, Slowikowska-Hilczner J, Kliesch S, Behre HM, Krausz C, Goulis DG, Jørgensen N. Testicular Biopsies in Adolescent and Adult Andrological Patients: The EAA Clinical Guidelines. *Andrology*. 2026 Jul 20. <https://doi.org/10.1111/andr.70300>

A multicentre controlled trial examined the effect of letrozole (aromatase inhibitor) in men with spermatogenic failure (predominantly NOA). After 3 months, 14.3% of participants treated with letrozole plus vit. C and E achieved an upgrade in sperm concentration category compared with 5.4% in those receiving vitamins alone. Aromatase inhibition can be considered for treating NOA or severe oligozoospermia before getting into more invasive modes of treatment.



Sun Y, Yao C, Liu G, Li Z, *et al. et.* Bu X, Qian D, Wu S, Qiu Y, Li Z, Li P. Letrozole and Infertility Among Males With Spermatogenic Failure: A Randomized Clinical Trial. *JAMA Netw Open*. 2026 Jun 1;9(6):e2618422. <https://doi.org/10.1001/jamanetworkopen.2026.18422>

The RANKL pathway, composed of RANKL, its receptor RANK, and the decoy receptor osteoprotegerin (OPG), is predominantly active in bone, but it is also expressed in the male reproductive system. A controlled trial examined the effects of targeting this pathway in infertile men using inhibitor denosumab.



The first study reassured that denosumab had no effect on glucose- or lipid homeostasis but induced a small increase in serum alanine aminotransferase in young infertile men with no serious co-morbidities. The second study found a correlation between OPG and minerals in seminal fluid, but the levels were not affected by a short-term denosumab.

Wriedt EB, Jorsal MJ, Yahyavi SK, Juel Mortensen L, Eldrup E, Juul A, Holt R, Blomberg Jensen M. Effects of a single-dose denosumab on glucose and lipid homeostasis in young infertile men. *Endocrine*. 2026 Jun 25;91(1):215. <https://doi.org/10.1007/s12020-026-04683-8>

Yahyavi SK, Jorsal MJ, Wriedt EB, Jørgensen N, Juul A, Holt R, Blomberg Jensen M. Osteoprotegerin is strongly associated with calcium and magnesium in seminal fluid but not affected by denosumab. *J Endocrinol Invest*. 2026 Jul 24. <https://doi.org/10.1007/s40618-026-02996-z>

This meta-analysis of 28 studies found a clinically relevant association between low circulating testosterone (T) levels and the metabolic dysfunction-associated steatotic liver disease (MASLD).

T deficiency appears independently linked to MASLD onset and severity beyond the effects of age and adiposity. SHBG levels were also relatively lower in men with MASLD. Attending clinicians ought to perform reciprocal screening of liver health and gonadal status in at-risk men.

Spaggiari G, Valentina LD, Felicani C, Gabrielli F, Lugari S, Corona G, Ventura P, Simoni M, Nascimbeni F, Santi D. The Bidirectional Association Between MASLD and Male Hypogonadism: An Updated Meta-Analysis. *Andrology*. 2026 Jul 9. <https://doi.org/10.1111/andr.70305>

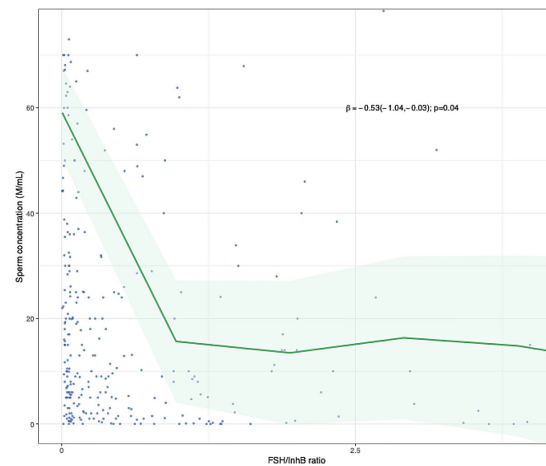


The authors investigated the role of the FSH/Inhibin B ratio as a marker of spermatogenesis impairment severity in primary infertile men with low testosterone (tT). Men with a higher FSH/Inhibin B ratio exhibited a more severe phenotype, characterized by reduced Inhibin B production at comparable FSH levels, which is associated with impaired gonadal function.

Negri F, Pozzi E, Raffo M, Boeri L, Birolini G, Eisenberg ML, Montorsi F, Salonia A. Follicle-Stimulating Hormone to Inhibin B Ratio Among Primary Infertile Men With Low Testosterone-A Biochemical Marker of Testicular Reserve.

Andrology. 2026 Jul 17.

<https://doi.org/10.1111/andr.70321>

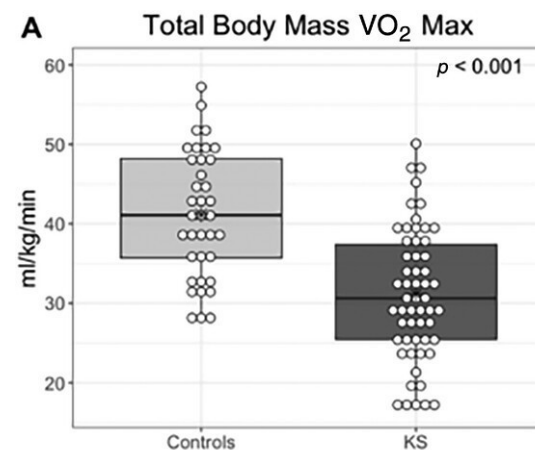


This study examined cardiorespiratory fitness (CRF) and other biomarkers of cardiometabolic health in adolescents and young adults with XXY Klinefelter syndrome. Compared with controls, CRF was markedly reduced in XXY, with 24% lower peak VO_2 , driven primarily by excess adiposity. The study identified an underrecognized target for early intervention to reduce cardiometabolic risk.

Swenson K, Bothwell S, Middleton A, Tartaglia NR, Zeitler PS, Nadeau KJ, Davis SM. Impaired Cardiorespiratory Fitness in Adolescents and Young Adults With 47,XXY/Klinefelter Syndrome.

Andrology. 2026 Jul 23.

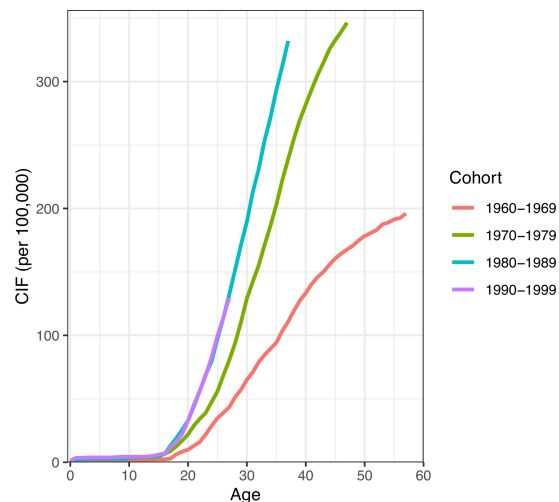
<https://doi.org/10.1111/andr.70307>



A nationwide cohort study of men born in Finland between 1960 and 1999 demonstrated a significant increase in the incidence of testicular cancer across birth cohorts, peaking among men born in 1975–1979. Marked geographic clustering was observed, with an eastward shift in higher incidence. These findings support the hypothesis that prenatal environmental factors contribute to the pathogenesis of testicular cancer.

Kaipia A, Seppä K, Hirvonen E, Mäkinen E, Malila N, Pitkaniemi J, Toppari J, Boström P, Seikkula H. Geographical Pattern of Testicular Cancer Points to Maternal Exposures Behind Increasing Incidence. **Int J Cancer.** 2026 Jul 4.

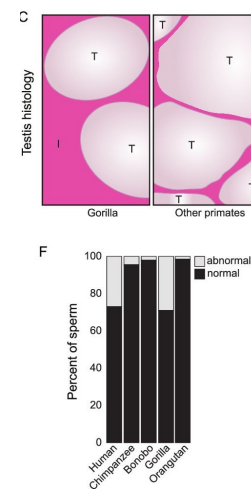
doi: [10.1002/ijc.70636](https://doi.org/10.1002/ijc.70636)



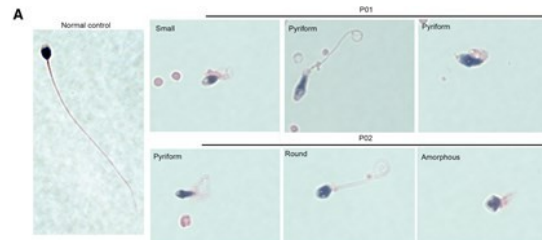
Androgenetics

This fascinating study explained why polygynous gorillas have relatively small testicles and produce lower-quality sperm than other primates. The team examined patterns of natural selection across species and identified in gorillas genome-wide signatures of relaxed purifying selection in genes associated with testis development and sperm function. They identified numerous new genes and confirmed their function in sperm production and fertility in fruit flies. The novel gene patterns may help identify new diagnostic markers and therapeutic targets for male infertility.

Bowman JD, Silva N, Schüftan E, Almeida JM, Brattig-Correia R, Oliveira RA, Tüttelmann F, Enard D, Navarro-Costa P, Lynch VJ. Pervasive relaxed selection on spermatogenesis genes coincident with the evolution of polygyny in gorillas. *ELife*. 2026 Jul 7;13:RP94563. <https://doi.org/10.7554/elife.94563>



Biallelic *CAMSAP1* (calmodulin-regulated spectrin-associated protein 1) variants were identified in 3 Asian individuals. Their sperm displayed multiple abnormalities in sperm flagella (MMAF phenotype) and diverse head abnormalities. Mechanistically, CAMSAP1 associates with CALM1 and SPTBN1 to couple manchette microtubules with the perinuclear spectrin-actin network.



Zheng R, Yan J, Zhi W, Huang G, Du X, Zhang H, Shaiq PA, Tan Y, Tu C, Shi Q, Xu W. Bi-allelic mutations of *CAMSAP1* result in teratozoospermia with sperm head and flagella defects in humans. *Hum Reprod*. 2026 Jul 1;41(7):1062-1077. <https://doi.org/10.1093/humrep/deag071>

Translational and basic andrology

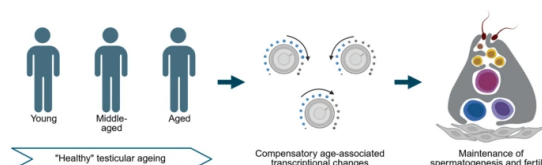
Does the father's nutrition state affect the offspring? This excellent study demonstrated in the mouse model that paternal diet influences paternal gut microbiome and testicular gene expression profile (incl. Wnt pathway), without affecting fertility.



Importantly, specific pre-fertilisation dietary regimens induced significant changes in fetal growth of the offspring and placental gene expression in a sex-specific manner.

Morgan HL, Eid N, Holmes N, Carlile M, Henson S, Sang F, Wright V, Castellanos-Urbe M, Khan I, Nazar N, May ST, Mitchell RT, Lopes F, Robinson RS, Coppi AA, Batra V, Watkins AJ. Paternal over- and under-nutrition programme fetal and placental development in a sex-specific manner in mice. *ELife*. 2026 Jul 20;15:RP109392. <https://doi.org/10.7554/eLife.109392.4>

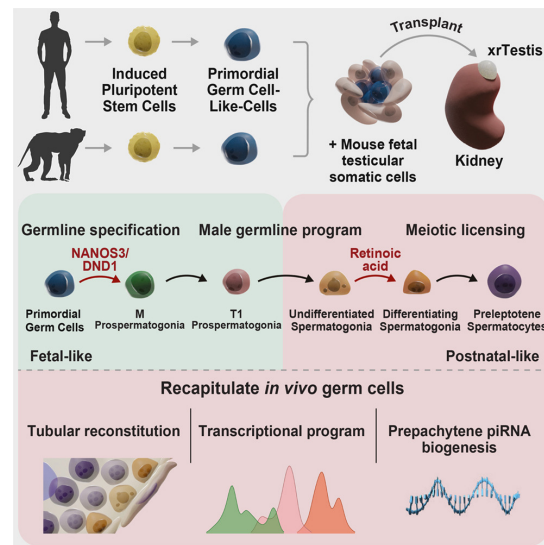
This excellent study analysed transcriptomic dynamics of the ageing human testis in samples with full spermatogenesis from men of different age.



The ageing was associated with widespread alternative splicing events and significant transcriptional changes, particularly associated with metabolic pathways, inflammation, oxidative stress, including some genes involved in the formation of double-strand breaks (DSBs) and DNA repair during early meiosis. The authors suggest that these changes might be compensatory to help preserve reproductive capacity.

Wang Y, Berres S, Krenz H, Tekath T, Wöste M, Sandmann S, Körtje A, Henrich A, Terwort N, Tüttelmann F, Neuhaus N, Kliesch S, Wistuba J, Gromoll J, Laurentino S. Normal spermatogenesis in older men is associated with compensatory transcriptome changes. *GeroScience*. 2026 Jul 14. <https://doi.org/10.1007/s11357-026-02403-8>

The Sasaki lab reported further progress in differentiating human and macaque spermatogonia-like cells from induced pluripotent stem cells (iPSCs). The team combined previously produced from iPSC primordial germ cell-like cells with mouse fetal testicular cells, obtaining self-organized xenogeneic reconstituted testis (xrTestis), containing tubule-like structures. Subsequent transplantation of xrTestes into immunodeficient mice resulted in generation of spermatogonia-like cells up to meiotic onset, including prepachytene piRNA biogenesis and rare preleptotene spermatocytes.



Whelan EC, Guo M, Yokomizo R, Seita Y, Hwang YS, Shirafuta Y, Leu NA, Cheng K, Ahrend F, Haase AD, Sasaki K. Generation of spermatogonia from human and non-human primate pluripotent stem cells. *Cell Stem Cell*. 2026 Jul 10:S1934-5909(26)00229-8. <https://doi.org/10.1016/j.stem.2026.06.001>

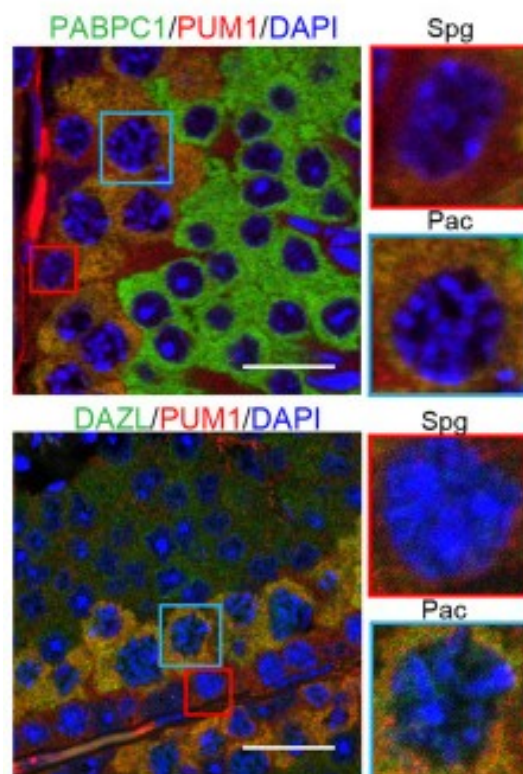
Germ line genome architecture was investigated in a marsupial (tammar wallaby) and a reptile (bearded dragon) in comparison with mouse, using in situ chromosome capture conformation (Hi-C) and single-cell RNA sequencing.



The authors uncovered lineage-specific chromatin folding patterns in germ cells and inter-chromosomal interactions during meiosis, including meiotic sex chromosome inactivation. The findings provided novel insights into the evolution of germ line chromatin architecture.

Marín-Gual L, Álvarez-González L, González-Rodelas L, Coppen F, Milton AM, O'Neill RJ, Pask AJ, Renfree MB, Georges A, Waters PD, Ruiz-Herrera A. Divergent 3D genome architecture of male germ cells across vertebrates. *Nat Commun*. 2026 Jun 20. <https://doi.org/10.1038/s41467-026-74695-5>

Post-transcriptional regulation of chromatin remodelling during spermatogenesis was investigated in the mouse. The study showed that the RNA-binding proteins PUMILIO1 (PUM1) and PUMILIO2 (PUM2) promote translation of mRNAs encoding chromatin regulators. Conditional deletion of *Pum1* and *Pum2* in germ cells resulted in male sterility, with spermatogenic failure and impaired histone-to-protamine exchange. Mechanistically, PUM1/2 associate with DAZL and PABPC1 to form a germ cell-specific translational activation complex.

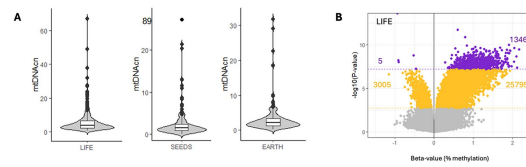


Zang M, Liu S, et al. et Lin K, Xu EY. PUM1 and PUM2 promote translation of chromatin regulators to ensure mammalian spermatogenesis. *Sci Adv*. 2026 Jul 17;12(29):eaed5708. <https://doi.org/10.1126/sciadv.aed5708>

The association between sperm mitochondrial DNA copy number (mtDNAcn) and genome-wide DNA methylation was investigated in men from a general population and two infertility cohorts and found that higher sperm mtDNAcn was associated with DNA hypermethylation.

Differentially methylated CpGs were enriched in the regulation of male meiosis and spermatogenesis pathways, and early embryonic development.

Sawant S, Nowak K, Paskavitz AL, Houle E, Bertolla RP, Minguez-Alarcon L, Hauser R, Pilsner JR. Sperm Mitochondrial DNA Copy Number and Nuclear DNA Methylation Across Clinical and Non-Clinical Preconception Cohorts. *Andrology*. 2026 Jul 20. <https://doi.org/10.1111/andr.70320>



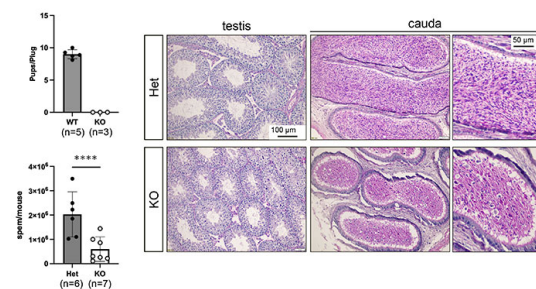
The function of perinuclear germ-cell actin-related protein T2 (ACTRT2) was investigated in this mouse study. Actrt2-deficient mice displayed male subfertility with pronounced acrosomal malformations.

The authors proposed that ACTRT2 is a structural component of the perinuclear theca, stabilizing the acroplaxome during spermiogenesis and acrosome biogenesis by modulating actin dynamics.

Kovacevic A, Ordziniak E, Hinterlang LD, Arevalo L, Merges GE, Schneider S, Schorle H. Loss of perinuclear theca protein ACTRT2 causes subfertility and acrosome destabilization in mice. *bioRxiv* [PREPRINT] 2026, June 9, doi: <https://doi.org/10.64898/2026.06.05.730397>

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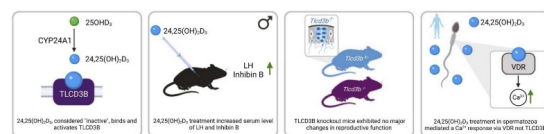
This study examined the role of gangliosides in spermatogenesis by generating KO mice for beta-1,3-galactosyltransferase 4 (B3galt4). KO males were infertile but had normal size testis. Abnormalities were observed during the late stages of spermatogenesis, including a reduced number of elongating/elongated spermatids. Few sperm recovered from the cauda epididymis had morphological abnormalities and impaired motility.



Nagata S, Nishioka S, Ikawa M, Ozawa M. B3GALT4-dependent gangliosides are required for normal late spermatogenesis and male fertility. *J Reprod Dev*. 2026 Jul 16. <https://doi.org/10.1262/jrd.2026-089>

Vitamin D is metabolized to long considered “inactive” 24,25(OH)₂D₃, recently found as the activator of TLCD3B, which in this study was localized in the midpiece of spermatozoa.

Treatment with 24,25(OH)₂D₃ increased serum LH and inhibin B in male mice and elicited a rapid Ca²⁺ increase in human spermatozoa. TLCD3B-deficient male mice, however, showed no changes in reproductive function.



Kooij I, Mitrofanov K, Rehfeld A, Andreassen CH, Kyhn Madsen S, Janssen AM, St-Arnaud R, Jørgensen A, Blomberg Jensen M. The 24,25(OH)₂D₃-TLCD3B signaling complex and reproductive function in mice and men. *J Steroid Biochem Mol Biol*. 2026 Jun 28;264:107060. <https://doi.org/10.1016/j.jsbmb.2026.107060>

New research resource

A new open resource for endocrinology research, **Hormone Cell Atlas** (hormonecellatlas.org.uk) has been created! Fei *et al.* systematically investigated the production and action of more than 162 hormones and their receptors across 47 human tissue types at cellular resolution.



Of relevance for andrologists, the tissue types in the Atlas include the testis and prostate (but not yet epididymis). In their lead *Science* study, the authors reported some novel aspects, f. ex. widespread hormone expression in immune cells (secretin in dendritic cells), or unexpected cross-talk between endocrine axes traditionally viewed as independent (gastric polypeptides and their receptors present in cardiomyocytes).

Fei L, Huang-Doran I, Lawler K, Yu Y, Pett JP, Méndez-Acevedo KM, Shah D, Margalef-Rieres J, Pohlman JS, Cakir B, Moy MR, Legg RG, Xu C, To K, Pham D, Predeus AV, Hanssen R, Cacciottolo TM, Kapuge RK, Polanski K, Oliver AJ, Teichmann SA, Farooqi IS. A Hormone Cell Atlas maps the human endocrine system at cellular resolution. *Science*. 2026 Jul 2;393(6806):eae2672
[DOI: 10.1126/science.aeb2672](https://doi.org/10.1126/science.aeb2672)

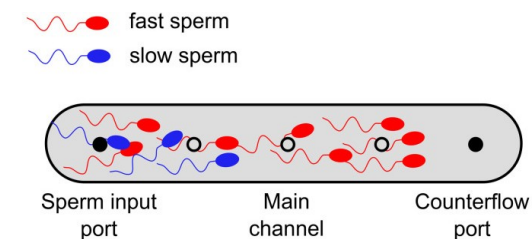
Andrology lab

Three methods of sperm isolation were compared in this study: electrophoretic separation (the Felix system), sperm swim-up, and density gradient centrifugation (DGC), using a novel assay that allowed assessing vitality and DNA fragmentation simultaneously in the same spermatozoon.

The Felix system and swim-up both outperformed DGC in both, fresh and cryopreserved sperm.

Aitken, RJ, S. Lambourne, A. Sheridan, H.W. Bakos, "Comparison of Different Sperm Isolation Strategies for Fresh and Cryopreserved Human Spermatozoa Using a Simple Method for Simultaneously Assessing Sperm Vitality and DNA Fragmentation." *Andrology* (2026): <https://doi.org/10.1111/andr.70282>

A new "must-have" for spermatology labs: a "sperm racetrack"! The andrology and mechanical engineering teams at the Utah University jointly built a microfluidic device that races sperm against each other.



The device separates sperm according to speed, which may prove useful to study the genetic and physiological causes of sperm immotility, and swimming-based sperm segregation distorters in humans. The sperm racetrack may also serve as a tool for enriching fast-swimming sperm for assisted reproductive technologies.

Baldwin-Brown J, Hulse L, Nepal S, Ullah A, Saha U, Aston KI, Gale B, Phadnis N. A sperm racetrack to separate sperm by swim speed. *Lab Chip*. 2026 Jul 2. doi: 10.1039/d6lc00399k. <https://doi.org/10.1039/d6lc00399k>

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